

Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder

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Summary To determine safety and the efficacy of carnitine treatment in children with attention-deficit hyperactivity disorder (ADHD). The ADHD behavior was observed by parents completing the Child Behavior Checklist (CBCL) and by teachers completing the Conners teacher-rating score, in a randomized, double-blind, placebo-controlled double-crossover trial. In 13/24 boys receiving carnitine, home behavior improved as assessed with the CBCL total score ($P < 0.02$). In 13/24 boys, school behavior improved as assessed with the Conners teacher-rating score ($P < 0.05$). Before treatment, the CBCL total and sub-scores were significantly different from those of normal Dutch boys ($P < 0.0001$). Responders showed a significant improvement of the CBCL total scores compared to baseline ($P < 0.0001$). In the majority of boys no side effects were seen. At baseline and after carnitine treatment, responders showed higher levels of plasma-free carnitine ($P < 0.03$) and acetylcarnitine ($P < 0.05$). Compared to baseline, the carnitine treatment caused in the responsive patients a decrease of 20–65% (8–48 points) as assessed by the CBCL total problem rating scale. Treatment with carnitine significantly decreased the attention problems and aggressive behavior in boys with ADHD. © 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The attention-deficit hyperactivity disorder (ADHD) is a neurobehavioral predominantly inheritable disorder with a spectrum of problematic behavior,¹ possibly caused by structural or functional abnormalities in the connections between the frontal cortex and the basal ganglia.² It is the most common psychiatric disorder in children and the symptoms often persist into adolescence and adulthood.² Available literature indicates an important role of stimulant medication in improving abnormal behavior, cognitive and social function in ADHD. The use of stimulating drugs may be associated with adverse side effects.³

Tricyclic antidepressants (TCA), non-TCA antidepressants, clonidine and bupropion are also used widely.

Improvement in behavior during treatment with these drugs is reported, having a mostly moderate and sometimes robust response.⁴

Preliminary experience in our hospital suggested that carnitine is a safe alternative drug to treat the condition. In two families we diagnosed a low plasma carnitine level (20 $\mu\text{mol/l}$) and ADHD behavior in four children. A trial treatment of these children with 100 mg carnitine/(kg day), twice daily, caused a decrease in their hyperactive impulsive behavior. After cessation of the carnitine medication, the abnormal behavior returned within 3–4 weeks, and reintroduction of carnitine improved their behavior again. Carnitine treatment also improved the condition of five other children with ADHD, who did not respond to methylphenidate or clonidine or other psychiatric treatment (unpublished data).

L-Carnitine is a small water-soluble molecule and has an important role in metabolism as carrier of activated fatty acids. It is indispensable for the oxidation of long-chain fatty acids by mitochondria, stimulates the oxidation of pyruvate and branched-chain 2-keto fatty acids and decreases acyl-CoA levels. Acetylcarnitine is a high-energy reservoir in equilibrium with the intracellular

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acetyl-CoA pool. Acetyl-CoA may be oxidized by the Krebs cycle for energy production, or act as acetyl donor for fatty acid synthesis or elongation, and for the synthesis of steroids and acetylcholine.

Arduini and co-workers demonstrated that the carnitine system is involved in membrane repair by acyl delivery in the cell, including the neurons.⁵ The transport of carnitine to the brain is a slow process due to a low affinity.⁶ PET studies in rats with labeled acetylcarnitine, showed that mainly carbon from acetyl is transported to the brain,⁷ and that the metabolism of the acetyl group in brain differs from that of glucose. Acetylcarnitine is more efficiently incorporated into polyunsaturated fatty acid, which is an important constituent of brain phospholipids.^{8,9}

In rodent brain, acetylcarnitine was reported to attenuate the neurological damage¹⁰ and to improve energy metabolism¹¹ after ischemia and reperfusion, to normalize the age-related impairment of several receptor systems¹² and the membrane phospholipid metabolism¹³ and also to treat hyperactivity.¹⁴

Recently, the hyperactive behavior of patients with the fragile X syndrome was successfully treated with 50 mg/(kg day) acetylcarnitine in a placebo-controlled study.¹⁵

The objective of this study was to whether the earlier observed effect of carnitine treatment could be confirmed in a controlled study of carnitine vs placebo in a new group of ADHD patients.

PATIENTS AND METHODS

This was a randomized, double-blind, placebo-controlled double-crossover study conducted at the pediatrics outpatient clinic. The double crossover design was chosen because, during pre-trial observations, cessation and reintroduction of carnitine was followed by deterioration and improvement in behavior, respectively. No carry-over effect was observed during pre-trial observations.

At first, the boys were screened and examined by the pediatrician. Then, the boys were extensively examined and interviewed by the child psychiatrist or child psychologist to confirm the ADHD diagnosis and to rule out any serious co-morbidity (psychosis, depression, autism).

The inclusion criteria were (1) boys aged between 6 and 13 years, outpatients living in a family home; (2) a diagnosis of ADHD according to DSM IV American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders)¹⁶ for the combined group with attention deficit/hyperactivity/impulsiveness based on the combined use of clinical interview of child psychiatrist, child psychologist and pediatrician according to their routine procedures and a Child Behavior Checklist (CBCL) score in the clinical area on the total score or at

least one the following sub-scores: attention problems, delinquency and aggressive behavior^{17,18} as recommended by the Dutch Psychiatric Association;¹⁹ (3) not receiving any stimulant medication; (4) attending normal elementary school; (5) healthy on physical examination and laboratory tests; (6) written informed consent was obtained from the parents.

The exclusion criteria were (1) heart disease, impaired renal function (plasma creatinine >70 μ mol/l), impaired liver function (plasma γ -GT >40 U/l), diabetes mellitus; (2) treatment with β_3 -sympatico-mimetics and/or parasympatholytics for chronic obstructive lung disease and bronchial asthma; (3) important changes in school or home situation expected during the course of the study period; (4) psychosis or severe brain damage or other serious psychiatric disease as assessed by the child psychiatrist or psychologist; (5) any concomitant disease that might interfere with drug evaluation; (6) participation in another pharmacological study or treatment with carnitine within 1 month prior to the screening visit. Before this trial, no boy received any carnitine treatment.

Instruments and measures

As there is no objective diagnostic marker for ADHD,^{1,2} the CBCL total problem score, the CBCL attention problems sub-score, the CBCL delinquency sub-score, the CBCL aggressive behavior sub-score were used to follow the condition of the boys as assessed by the parents. According to the CBCL manual, recommending to use the total-rating score in complex behavior disorders for research purposes, the total-rating score was completed every 8 weeks. The CBCL checklist contains 120 questions with three grades of severity, and is completed by the parents. The CBCL was used to distinguish a child's behavior into normal and abnormal clinical behavior. The threshold of clinical behavior of the CBCL total problem score is above 40 points, that of the attention problem, the delinquency and aggressive behavior sub-scores is above 10, 5 and 20 points, respectively. These sub-scores match the DSM IV criteria according to the CBCL manual. For each boy, the response over time was assessed compared to baseline and a 30% decrease of the CBCL rating scale or a decrease below the clinical area was considered a responder.

The Conners Teacher 39 item rating scale was used.²⁰ The Conners Teacher rating scale (CTRS) analyses all behavior problems in the school situation and contains 39 items with four grades of severity. The scale was developed as a diagnostic tool and to assist at the evaluation of attention/behavior disorders. To use the rating scale as a treatment intervention tool to detect attention/behavior differences, the grades of severity are analyzed as ordered categories. A child was considered as

a responder if there was a 30% decrease in the number of most severe ratings (degree 4) in a carnitine period compared to the baseline period. Each boy was assessed at the end of each trial period for the three trial periods separately.

Procedure

Approval was received for the study from the Medical Ethical Committee of the Westfries Gasthuis, Hoorn, The Netherlands. The duration of the trial was 24 weeks. Written informed consent was obtained from the parents. At the first visit 30 boys were screened, 26 patients were included in the trial as they appeared, at the pediatric outpatient department, fulfilling the inclusion criteria. These 26 eligible boys were randomly assigned, in blocks of six, to two groups. There were two groups of 13 boys each. One group received placebo–carnitine–placebo and the other group carnitine–placebo–carnitine. The three treatment periods were 8 weeks each. At the end of each period, all patients visited the pediatrician for examination. No other medication for co-morbidity was given during the entire study. Blood samples for laboratory tests were taken at all visits except the first one. All patients received psychological counseling during and after the trial.

Medication

The investigated drug was L-carnitine, stored in drinking vials of 6 g/20 ml; the placebo had a similar look and taste. The medication was taken twice daily after meals. The carnitine dosage was 100 mg/kg daily with a maximum of 4 g. The quantity of medication was supplied for a period of 8 weeks and every 8 weeks a new quantity of medication was supplied. The remaining medication was collected by the pediatrician, and indicated a good patient compliance by calculating the difference. For emergency purposes, the investigator kept a set of codes in sealed opaque envelopes.

Safety evaluation follow-up

Laboratory tests were done at screening, in week 8, 16, and 24 for hemoglobin, hematocrit, red blood cell count, white cell count, white cell differential count, platelet count and the plasma levels of urea, creatinine, sodium, potassium, ASAT, ALAT, γ -GT, alkaline phosphatase, and free and acetylcarnitine.²¹ Physical examination was done at screening and in week 24.

Statistical analysis

The null hypothesis is that there is no difference in the number of responders in the placebo and carnitine period

in a trial period of 8 weeks. Data analysis was done with Microsoft Excel 2000 and statistical analysis with STATA 7. The McNemar χ^2 -test was used to compare the number of responders in the carnitine and placebo period. The two-sample *t*-test was used to calculate the significance of the difference in the CBCL total problem scores and sub-scores, and in the plasma-free carnitine and acetylcarnitine levels between responders and non-responders at baseline and after carnitine. A difference with a *P* of 0.05, or smaller, was considered to be significant.

RESULTS

The trial profile is presented in Figure 1. One boy dropped out in the first placebo period because of familial circumstances; a second one in the first carnitine period because a pungent skin odor was encountered. The baseline CBCL clinical characteristics and plasma carnitine levels of the 26 boys are described in Tables 1 and 2. Twenty-two boys completed the three trial periods and 24 boys completed the first two periods. Two boys completed only the first two periods, one boy fainted and the other due to personal reasons. On request of the parents, these two boys were treated with carnitine in the post-trial period. After 6 months, the behavior of both boys improved to a non-clinical level as judged by the CBCL total score.

The CBCL-baseline ratings (Table 1) showed total-problem scores and sub-scores for attention problems, delinquency and aggressive behavior, that are significantly different from the normal Dutch boys.¹⁸

On the CBCL-rating scale, 13 boys were found to be a responder ($P < 0.02$). On the CTRS, 12 boys were found to be a responder ($P < 0.02$) (Table 3). Comparing the two rating scales, 11 boys were found to be a responder on both scales during the carnitine period. Compared to baseline, responders showed a highly significant improvement of the CBCL total scores ($P < 0.0001$) and the CBCL sub-scores of attention problems ($P < 0.0001$), delinquency ($P < 0.01$) and of aggressive behavior ($P < 0.0001$), Non-responders showed no improvement (Table 4).

Plasma-free carnitine levels were significantly different between responders and non-responders after treatment ($P < 0.03$). Plasma acetylcarnitine levels were also significantly different between responders and non-responders after treatment ($P < 0.05$) (Table 5).

The overall effect of the carnitine treatment compared to baseline was a decrease of 20–65% (8–48 points) of the baseline ratings as assessed by the CBCL-total-problem rating scale.

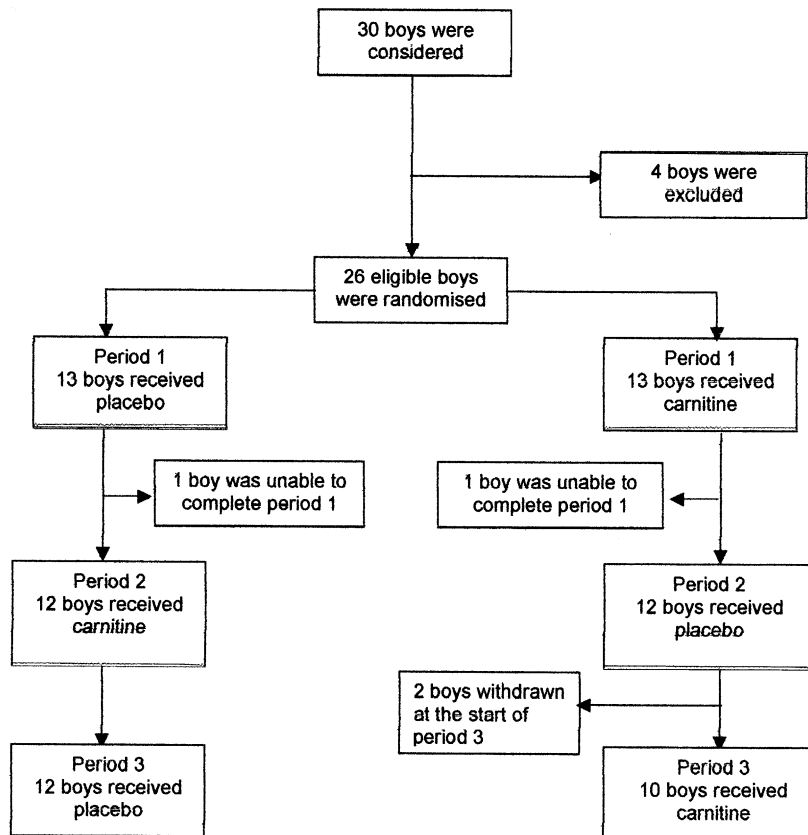


Fig. 1 Trial profile.

Table 1 CBCL scores of normal Dutch boys^a and of the patients before treatment

CBCL	Normal Dutch boys (n=579)		Patients before trial (n=26)		P
	Mean (SD)	Range	Mean (SD)	Range	
Total score	21.3 (14.0)	0–40	68.8 (20.3)	30–101	< 0.0001
Attention problems	3.2 (2.8)	0–10	10.8 (2.6)	7–15	< 0.0001
Delinquency	1.3 (1.4)	0–5	3.5 (2.9)	0–11	< 0.001
Aggressive behavior	7.0 (5.4)	0–20	23.1 (5.8)	14–36	< 0.0001

^aCBCL scores of normal Dutch boys are from Verhulst et al. [18].

Table 2 Plasma-free carnitine and acetylcarnitine in the patients before treatment

n=26	Mean (SD)	Range
Free carnitine (μmol/l)	42.6 (7.8)	25.2–57.3
Acetylcarnitine (μmol/l)	4.8 (1.2)	2.9–8.4

Table 3 Summary of the number of responders

Medication	CBCL-rating scale	CT-rating scale
Number of patients=24		
Carnitine	13 (54%)	12 (50%)
Placebo	2 (13%)	4 (17%)
χ^2	4.76	4.00
df	1	1
P <	0.02	0.05

Adverse events

Two boys broke their arm due to their hyperactive behavior during the placebo period. One boy had a short unexplained period of fainting a few days after the onset of the placebo period following carnitine. No explanation was found. One boy had an elevated plasma creatinine

level during the last placebo period, but 2 weeks after the trial, a normal level was found. Physical examination of all boys by the pediatrician at the end of the three trial periods showed no abnormalities. One patient observed

an unpleasant body odor during treatment with carnitine, a well-known side effect, likely due to the formation of trimethylamine. No other child in the trial showed this problem. Although we observed in some other patients that this phenomenon disappeared with riboflavin medication (unpublished data), such an intervention was not part of this study protocol.

DISCUSSION

After finishing the three trial periods, 20/24 boys continued the carnitine medication on their parents' request. Continued use during 6 months resulted in a normal non-clinical behavior of 19 boys as judged by their parents and teachers. In 11 boys this was assessed by the standard-rating scales, and in nine boys by global assessment. On parents request the medication was continued in 2 boys.

In the last decade, new roles of the carnitine system have been recognized²² such as stimulation of the microcirculation,²³ membrane repair by reacylation of phospholipids,⁵ and the mitochondrial elongation-desaturation of (n-3) fatty acids to docosahexaenoic acid.^{24,8} In view of the latter finding, it is of interest that the concentration of this fatty acid, which is important for brain maturation and functioning, is decreased in plasma of ADHD patients.²⁵ Some investigators consider ADHD

and its comorbidity, as a disorder of fatty acid and phospholipid metabolism.²⁶

We hypothesize that carnitine stimulates the synthesis of both acetylcholine and docosahexaenoic acid in certain areas of the brain involved in ADHD patients.

Limitations

We acknowledge the limitations of this pilot study, because only a small number of boys were included, and of the many aspects of ADHD behavior, only the behavior was assessed by the CBCL- and the CTRS-rating scales.

Clinical implications

Given twice daily, carnitine appeared to be effective and well tolerated for the treatment of a group of children with ADHD, that showed a significantly abnormal behavior compared to normal Dutch boys. A larger scale study will be done to investigate the effect of treatment on the many more biochemical and psychological aspects of ADHD behavior.

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Table 4 CBCL scores of responders and non-responders during the trial

	Mean (SD)	Range	P vs. baseline
Responders receiving carnitine <i>n</i> =13			
Total-problem score	33.9 (6.6)	23–47	<0.0001
Attention problems	6.6 (2.9)	3–13	<0.0001
Delinquency	1.3 (1.4)	0–4	<0.01
Aggressive behavior	12.7 (5.5)	7–23	<0.0001
Non-responders receiving carnitine <i>n</i> =8			
Total-problem score	65.7 (22.7)	36–94	=0.4
Attention problems	10.5 (3.0)	7–15	=0.4
Delinquency	4.1 (2.9)	1–9	=0.7
Aggressive behavior	22.0 (6.8)	14–30	=0.3

Table 5 Levels of plasma-free carnitine and acetylcarnitine in responders and non-responders

	Responders (<i>n</i> =13)		Non-responders (<i>n</i> =8)		Difference <i>P</i>
	Mean (SD)	Range	Mean (SD)	Range	
Plasma-free carnitine levels (μmol/l)					
Before treatment	42.3 (7.5)	32.2–57.3	39.3 (8.1)	25.2–49.1	0.2
After carnitine	81.0 (13.2)	62.5–106	68.9 (11.9)	49.6–84.1	<0.03
Plasma acetylcarnitine levels (μmol/l)					
Before treatment	4.8 (1.9)	3.5–8.4	4.4 (1.1)	2.9–6.4	0.3
After carnitine	11.8 (4.6)	5.6–18.5	8.6 (2.9)	3.9–13.7	<0.05

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